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Ambient Water Quality Criteria 2,4-Dimethyphenol

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2,4-DIMETHYPHENOL

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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CRITERION DOCUMENT
2,4-DIMETHYLPHENOL

Criteria

Aquatic Life

For 2,4-dimethylphenol, the criterion to protect freshwater aquatic life, as derived using the Guidelines, is 38 ug/l as a 24-hour average and the concentration should never exceed 86 ug/l at any time.

For saltwater aquatic life, no criterion for 2,4-dimethylphenol can be derived using the Guidelines and there are insufficient data to estimate a criterion using other procedures.

Human Health

Due to a lack of sufficient definitive data on mammalian toxicology and human health effects, a criterion to protect human health from toxic effects due to exposure to 2,4-dimethylphenol ingested through water and through contaminated aquatic organisms cannot be set at this time. In order to protect public health, exposure to this compound should be minimized as soon as possible.

BIBLIOGRAPHIC INFORMATION

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Ambient Water Quality Criteria: 2,4-Dimethyphenol.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for 2,4-dimethylphenol(2,4-xylenol). It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standar, ...

KEYWORDS: *Water quality, *Toxicology, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Xylenols.

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Introduction

2,4-dimethylphenol (2,4-DMP) is a natural product derived from coal and petroleum sources. 2,4-DMP finds use commercially as an important chemical feedstock or constituent for the manufacture of a wide range of commercial products for industry and agriculture. 2,4-Dimethylphenol is used in the manufacture of phenolic antioxidants, disinfectants, solvents, pharmaceuticals, insecticides, fungicides, plasticizers, rubber chemicals, polyphenylene oxide, wetting agents, and dyestuffs, and is an additive or constituent of lubricants, gasolines, and cresylic acid.

Although no direct commercial application for 2,4-DMP appears to exist presently, its wide use as a chemical intermediate, its toxicity to aquatic life, and its carcinogenic effect in mammals clearly indicate the potential hazard of 2,4-DMP to aquatic and terrestrial life.

2,4-Dimethylphenol (2,4-DMP) is a naturally occurring, substituted phenol derived from the cresol fraction of petroleum or coal tars by fractional distillation and extraction with aqueous alkaline solutions (U.S. EPA, 1976; Lowry, 1963; Gruse and Stevens, 1942; Rudolfs, 1953). 2,4-DMP is also known as m-xylenol, 2,4-xylenol or m-4-xylenol, and has the empirical formula $C_8H_{10}O$ (Weast, 1972).

Five other positional isomers of dimethylphenol or xylenol exist and include 2,3-, 2,5-, 2,6-, 3,4-, and 3,5-dimethylphenol. Since these isomers result from the different positioning of the two methyl groups on the phenol ring,

they are referred to as positional isomers. As would be expected, variations in their physical, chemical, and biological properties exist.

2,4-DMP has a molecular weight of 122.17 and in its normal state exists as a colorless, crystalline solid (Weast, 1972; Bennet, 1974). It has a melting point of 27 to 28 degrees C, a boiling point of 210 degrees C (760 mm Hg), a vapor pressure of 1 mm Hg at 52.8 degrees C, and a density of 0.9650 at 20 degrees C (Weast, 1972; Bennet, 1974; Jordan, 1954).

2,4-DMP is slightly soluble in water and as a weak acid (pka-10.6) it is also soluble in alkaline solutions (Sober, 1970). 2,4-DMP readily dissolves in organic solvents such as alcohol and ether (Weast, 1972).

2,4-DMP can be oxidized to form pseudoquinone (Rodd, 1952). However, the conditions required for this reaction generally are not found in the environment. 2,4-DMP reacts with aqueous alkaline solutions to form the corresponding salt. Such salts are readily soluble in water, provided that an alkaline pH is maintained. The free position on the aromatic ring, ortho to the hyroxyl group, may be alkylated (Kirk and Othmer, 1964) or halogenated (Rodd, 1952). However, such reactions under normal environmental conditions have not been reported.

The organoleptic properties of xylenols have been investigated. Hoak (1957) studied the threshold odor level of the various xylenols in water and reported that 2,4-dimethylphenol was detectable at a concentration of 55.5 ug/l at 30 degrees

C.; 2,4-DMP and other xylenols also have been reported to taint bream and common carp (Mitrovic, et al. 1973). Phenolic flavor may be acquired by fish flesh directly from water or indirectly from fish eating contaminated food or may be acquired by the tissues of other animals eating tainted fish (Mitrovic, et al. 1973).

Toxicity data on freshwater aquatic organisms for 2,4-DMP exist in the literature; however, there are no corresponding data on saltwater aquatic organisms. Studies have demonstrated acute toxic effects of 2,4-DMP on freshwater plants, invertebrates and vertebrate species. Chronic toxic effects have also been demonstrated in 2 freshwater vertebrate species. Studies on various species of freshwater microorganisms exposed to 2,4-DMP demonstrate either growth inhibition and/or lethality in the 2,4-DMP concentration range of 0.2×10^6 ug/l to 2.5×10^6 ug/l (Zsolnai, 1960; Laubenheimer cited by von Oettingen, 1949).

2,4-DMP demonstrates both oral and topical toxicity to several mammalian species at doses ranging from 809 mg/kg (oral LD50, mouse; Uzhdovini, et al. 1974) to 5,600 mg/kg (topical tumor formation, mouse; Boutwell and Bosch, 1959).

No data on mutagenic or teratogenic effects for 2,4-DMP on mammalian species were found in the literature. No reports of epidemiologic studies on workers exposed to 2,4-DMP or on a general population exposed to small amounts of 2,4-DMP which relate cancer incidence to exposure level were found.

Information regarding the concentration, persistence, fate and effects of 2,4-DMP in the environment is limited. However, its presence in petroleum fractions and coal tars, together with its use as a chemical feedstock or constituent for the manufacture of numerous products, clearly indicates the potential for both point and non-point source water contamination.

A large number of products utilize 2,4-DMP as a feedstock or constitutent. Hence, disposal of chemical and industrial process wastes and distribution from normal product applications represent feasible modes of entry of 2,4-DMP into the environment. Examples of the latter mode include pesticide applications, asphalt and roadway runoff, and the washing of dyed materials (U.S. EPA, 1975).

No quantitiative information is available on the presence of 2,4-DMP in industrial and municipal effluents, natural waters, soils and sediments, drinking water supplies, or finished drinking water.

Virtuallty no information is available on the persistence of 2,4-DMP in the environment. Nevertheless, the biooxidation of 2,4-DMP by Pseudomonas testosteroni grown on p-cresol has been reported by Dagley and Patel (1957). In addition, laboratory studies by Chapman (1971) demonstrated the ability of a strain of Pseudomonas sp. isolated from estuarine water to utilize 2,4-DMP as the sole carbon source in liquid enrichment cultures. Although the microbial metabolic pathways for the aerobic degradation of 2,4-DMP to B-ketoadipic acid

have been reported (Ornston and Stanier, 1966), these laboratory studies provide little information for its persistence in the environment. The complete biodegradation of 2,4-DMP has been reported to occur in approximately 2 months although the conditions were not stated (Rodd, 1952).

Although undissociated 2,4-DMP is highly soluble in non-polar solvents and should readily concentrate in organic films of polluted surface waters, no data are available to support this contention. Almost no information is available on its bioconcentration in plants or animals. Albersmeyer and Von Erichsen (1959) reported an accumulation of 16 to 17 mg 2,4-DMP in the crucian carp, Carassius vulgaris, after 6 hours of exposure to a concentration of 20,000 ug/l. Following the transfer of fish to toxicant-free water, the amount of retained 2,4-DMP was reduced to less than 10 mg and 5 mg after 1 and 3 hours, respectively. Bioconcentration studies (U.S. EPA, 1978) on the bluegill, Lepomis macrochirus, show a bioconcentration factor of 150 for 2,4-DMP with a biological half life of the compound in the tissue of less than 1 day. Results from both of these studies do not indicate a significant threat to aquatic life from 2,4-DMP residues. No 2,4-DMP residues have been reported in mammalian tissues.

Little information exists on the metabolism or excretion of 2,4-DMP by aquatic life, animals, or man. Bray, et al. (1950) studied the metabolism of orally administered 2,4-DMP and five other positional isomers in the female rabbit. All six isomers followed similar metabolic paths with 50 to 70 percent excreted as ether glucuronide, 8 to 16 percent excreted as ethereal sulfonate, and 1 to 3 percent excreted in the unconjugated form.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

A variety of data is available for freshwater aquatic life and 2,4-dimethylphenol with no observed adverse effects at concentrations as high as approximately 2,000 µg/l.

Acute Toxicity

The 96-hour LC50 value, obtained using flow-through conditions and measured concentrations, is 16,750 µg/l for juvenile fathead minnows (Table 1). The 192-hour LC50 obtained from this same exposure (Phipps, et al. manuscript) is 13,650 µg/l (Table 6) which indicates little additional mortality. The adjusted 96-hour LC50 value for the bluegill is 4,237 µg/l and the Final Fish Acute Value for these data is 2,200 µg/l.

The adjusted 48-hour EC50 value for Daphnia magna is 1,796 µg/l (Table 2) and when this concentration is divided by the sensitivity factor of 21 the result is the Final Invertebrate Acute Value of 86 µg/l. Since this result is lower than the comparable value for fish, it also becomes the Final Acute Value.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life (43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)) and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The 96-hour LC50 values for chlorinated phenols and bluegills (U.S. EPA, 1978) are directly related to the degree of chlorination. These values decrease from 6,590 ug/l for 2-chlorophenol and 3,830 ug/l for 4-chlorophenol to 60 and 77 ug/l for pentachlorophenol. These data and those for intermediate chlorinated phenols can be correlated with the n-octanol/water partition coefficient with a correlation coefficient of 0.95. Data for other species do not correlate as well.

Chronic Toxicity

An embryo-larval test (U.S. EPA, 1978) with the fathead minnow has been conducted and the chronic value derived from those results is 1,100 ug/l (Table 3). No chronic test with an invertebrate species has been performed. Since Daphnia magna appears to be more acutely sensitive than the fathead minnow or bluegill, a chronic test for this invertebrate species would probably be lower than the Final Fish Chronic Value and Final Chronic Value of 160 ug/l (Table 3).

Plant Effects

Huang and Gloyna (1967) exposed the alga, Chlorella pyrenoidosa, to 2,4-dimethylphenol and observed complete destruction of chlorophyll after 48 hours at a concentration of 500,000 ug/l (Table 4). Duckweed demonstrated chlorosis at a concentration of 292,800 ug/l (Blackman, et al. 1955) and this result is the Final Plant Value.

Residues

The bluegill was exposed for 28 days to ^{14}C-2,4-dimethylphenol (U.S. EPA, 1978) and the bioconcentration factor for whole-body is 150 (Table 5). The half-life in the bluegill is less than 1 day, which indicates that 2,4-dimethylphenol residues are probably not a potential hazard for aquatic organisms.

Miscellaneous

As stated earlier, the 192-hour LC50 value is 13,650 ug/l (Table 6). Since the 96-hour LC50 value obtained by the same investigators (Phipps, et al. manuscript) is 16,750 ug/l, there appears to be no appreciable cumulative mortality.

CRITERION FORMULATION

Freshwater -Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 2,200 ug/

Final Invertebrate Acute Value = 86 ug/l

Final Acute Value = 86 ug/l

Final Fish Chronic Value = 160 ug/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 290,000 ug/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 160 ug/l

0.44 x Final Acute Value = 38 ug/l

The maximum concentration of 2,4-dimethylphenol is the Final Acute Value of 86 ug/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 2,4-dimethylphenol the criterion to protect freshwater aquatic life as derived using the Guidelines is 38 ug/l as a 24-hour average and the concentration should not exceed 86 ug/l at any time.

Table 1. Freshwater fish acute values for 2,4-dimethylphenol

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	16,750	16,750	Phipps, et al. Manuscript
Bluegill, Lepomis macrochirus	S	U	96	7,750	4,237	U.S. EPA, 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 8,424 µg/l $\frac{8,424}{3.9}$ = 2,200 µg/l

Lowest value from a flow-through test with measured concentrations = 16,750 µg/l

Table 2. Freshwater invertebrate acute values for 2,4-dimethylphenol (U.S. EPA, 1978)

Organism	Bioassay Method *	Test Conc. **	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, Daphnia magna	S	U	48	2,120	1,796

* S = static

** U = unmeasured

Geometric mean of adjusted values = 1,796 µg/l $\frac{1,796}{21}$ = 86 µg/l

Table 3. Freshwater fish chronic values for 2,4-dimethylphenol (U.S. EPA, 1978)

Organism	Test *	Limits (ug/l)	Chronic Value (ug/l)
Fathead minnow, *Pimephales promelas*	E-L	1,500-3,200	1,100

* E-L = embryo-larval

Geometric mean of chronic values = 1,100 µg/l $\quad \frac{1,100}{6.7} = 160$ µg/l

Lowest chronic value = 1,100 µg/l

Table 4. Freshwater plant effects for 2,4-dimethylphenol

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Chlorella pyrenoidosa*	Complete destruction of chlorophyll after 48 hrs	500,000	Huang & Gloyna, 1967
Duckweed, *Lemna minor*	Chlorosis (LC50)	292,800	Blackman, et al., 1955

Lowest plant value = 292,800 µg/l

Table 5. Freshwater residues for 2,4-dimethylphenol (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
Bluegill, *Lepomis macrochirus*	150	28

Table 6. Other freshwater data for 2,4-dimethylphenol (Phipps, et al. Manuscript)

Organism	Test Duration	Effect	Result (ug/l)
Fathead minnow (juvenile), Pimephales promelas	192 hrs	LC50	13,650

Lowest value = 13,650 µg/l

SALTWATER ORGANISMS

Introduction

No data on the effects of 2,4-dimethylphenol on saltwater organisms are available.

CRITERION FORMULATION

Saltwater - Aquatic Life

CRITERION: For saltwater aquatic life, no criterion for 2,4-dimethylphenol can be derived using the Guidelines and there are insufficient data to estimate a criterion using other procedures.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

The compound 2,4-dimethylphenol is one of a group of substituted phenols which are derived from petroleum or coal tar acids. The compound also occurs naturally in plants and has been detected in tea, tobacco, and cigarette smoke.

The trivial name of the dimethylphenols is xylenol and is frequently reported as such in the literature. Throughout this document, dimethylphenol rather than xylenol, and methylphenol rather than cresol will be used. Cresol and cresylic acids will designate the complex mixtures produced commercially.

This document is intended to deal specifically with 2,4-dimethylphenol; however, three methylphenol isomers and six dimethylphenol isomers generally occur together in nature, in several industrial processes, commercial products, and phenolic wastes. It is unlikely that any large segment of the population would be exposed to 2,4-dimethylphenol alone. Because quantitative and qualitative data are not available for human exposure to 2,4-dimethylphenol, it is very difficult to establish a direct relationship between this compound and health effects in humans.

The six dimethylphenol isomers $(CH_3)_2\ C_6H_3OH$) are substituted derivatives of phenol; when the hydroxyl group is assigned the number one position, they are as follows: 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-dimethylphenol. The isomers can occur alone but are usually derived from fossil fuels as complex mixtures containing phenol, the three cresol isomers (2-, 3-, 4-methylphenol) and other substituted phenols. Commercial cresol and cresylic acids usually contain phenol, the three methylphenols, and the dimethylphenols. Some chemical and physical properties of the dimethylphenols are listed in Table 1.

These compounds are derived from petroleum or coal tar acids. The initial fractionation of petroleum or coal tar acids yields a complex mixture mainly composed of phenol, and methylated derivatives. In 1976, Klapproth, in reviewing cresols and cresylic acids, stated that dimethylphenols, methylphenols, and phenol are removed from petroleum in the naphtha-cracking process and are present in the spent caustic liquor used to wash petroleum distillate. Coal tar acids are obtained from coke oven byproducts, gas-retort oven tars, and distilled tar byproducts. It is estimated that 151 million pounds of cresol and cresylic acids were produced in the United States in 1975, down 21 percent from 1974. Cresol is used as a disinfectant, commercial degreasing agent, and in many manufacturing processes. The National Institute for Occupational Safety and Health (NIOSH, 1978) estimated that 11,000 people in the United States are occupationally exposed to cresol containing 2,4-dimethylphenol.

Considerable amounts of dimethylphenols are discharged in tar water from shale distillation along with oxybenzene,

TABLE 1

Some Physical and Chemical Properties of Dimethylphenol
Molecular Formula $(CH_3)_2C_6H_3OH$

Isomer, methyl	2,3-	2,4-	2,5-	2,6-	3,4-	3,5-
Molecular Weight	122.17	122.17	122.17	122.17	122.17	122.17
Boiling Point (^oC)	218	210	$211.5^{762\ mm}$	212	225	219 (Subliming
Melting Point (^oC)	75	27-28	75	49	66-68	68
Crystalline Form	Needles	Crystals	Needles	Leaflets	Needles	Crystals
Solubility in:						
Water	Slightly	Slightly	Soluble	Soluble	Slightly	Soluble
Ethyl Alcohol	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
Density[a]	-	0.9650 $20^o/4$	-	-	0.9830 $20^o/4$	0.9680 $20^o/4$

[a]Values e.g. $20^o/4$ means 20^oC, referred to water at 4^oC

(Handbook of Chemistry & Physics, 57th Edition. 1976.)

methylphenols and other phenolic compounds (Maazik, 1968). The dimethylphenol content of the waste material was reported to reach 22.1 percent of the total monohydric phenols in tar waters. According to data reported by the Tallin Polytechnical Institute, the River Purtse discharges about 800 kg of dimethylphenols daily into the Gulf of Finland (Maazik, 1968).

Methyl and dimethylphenols were found in relatively high concentrations in the water solubles from four fuel oils (Winters, et al. 1977). The fuel oils were refined in four different locations (Baytown, Texas; Baton Rouge, Louisiana; Billings, Montana; and Linden, New Jersey). The six isomers of dimethylphenol were present in the water solubles.

In whole animal studies with rats that received 1,3-dimethylbenzene orally, 2,4-dimethylphenol was the only phenolic metabolite reported in the urine (Bakke and Scheline, 1970). Approximately 2 percent of the dose was excreted as 2,4-dimethylphenol. The 2,6- and 3,5-dimethyl isomers were not detected. Jerina, et al. (1971) and Kaubisch, et al. (1972) presented data which showed that 2,4-dimethylphenol was the major metabolite produced in the metabolism of 1,3-dimethylbenzene by rat liver microsomes. The 2,6-dimethyl isomer was also a metabolic product; production of the 2,4-isomer was 10 times that of the 2,6-isomer. These studies suggest that metabolic pathways exist in the liver for the production of dimethylphenols from phenolic compounds which find their way into the blood stream.

Ingestion from Water

In 1975, Versar, Inc., prepared for the United States Environmental Protection Agency an initial assessment of the possible sources of 154 organic compounds which have been identified in drinking water supplies (Versar, 1975). In this document, the manufacturing point source of 2,4-dimethylphenol was designated as coal tar fractionation and coal processing. Commercial utilization of 2,4-dimethylphenol included: intermediate in the manufacture of phenolic antioxidants; pharmaceutical manufacturing; plastics and resins manufacturing; disinfectant (microbicide) manufacturing; solvent manufacturing; insecticides and fungicides, rubber chemicals, polyphenylene oxide, wetting agent, and dyestuffs manufacturing; cresylic acid constituent. The gross estimate of the United States annual discharge was 100 tons.

Small quantities were reported to be formed during sewage treatment (biological step) and biological degradation of municipal, biological and industrial wastes. There was no evidence that 2,4-dimethylphenol was formed during water purification; the report states that the compound is probably formed in small quantities (Versar, 1975).

Leachates from municipal and industrial wastes contained the compound and it was also formed by the degradation of high molecular weight tars and polymers. Anthropogenic non-point sources of 2,4-dimethylphenol were reported to be from asphalt and roadway runoff, the general use of pharmaceuticals, fuels, plastics, pesticides, washing of dyed materials and domestic sewage (Versar, 1975).

Biological treatment of wastes containing 2,4-dimethylphenol was reported to be 95 to 100 percent effective; activated carbon filtration 95 to 100 percent effective and incineration approximately 95 percent effective. The persistence of the compound in the environment was considered to be low, with complete degradation accomplished in approximately two months (Versar, 1975).

Pitter and Kucharova-Rosolova (1974) determined the biological degradability of 123 organic compounds; 2,4-dimethylphenol was 94.5 percent removed based on chemical oxygen demand (COD). The rate of degradation was 28.2 mg of 2,4-dimethylphenol removed per hour by a gram of the initial dry matter of biological inoculum. The percent of dimethylphenols removed based on COD ranged from 89.3 percent (for the 3,5-dimethyl isomer) to 97.5 percent (for the 3,4-dimethyl isomer). The rates of degradation ranged from 9.0 mg per gram inoculum per hour (for the 2,6-dimethyl isomer) to 35 mg per gram per hour (for the 2,3-dimethyl isomer).

Bad taste or odor in drinking water is often reported and has been ascribed to constituents of industrial wastes or microscopic organisms and decaying vegetation. Phenolic compounds are widely blamed for causing medicinal odors and tastes in water supplies. In 1957, Hoak determined the odor threshold of phenol and 19 phenolic compounds. Chlorinated phenols were the most easily detected; at 30°C, 2,4-dimethylphenol could be detected at 55.5 µg/l (Table 2).

TABLE 2

Odor Thresholds of Selected Phenolic Compounds

(Hoak, 1957)

Compound	Threshold Conc., ppb[a]	
	60°C	30°C
Phenol	5,000	10,000
2-methylphenol	25	71
3-methylphenol	100	383
4-methylphenol	200	45.5
2,4-dimethylphenol	100	55.5
2,5-dimethylphenol	11	33
3,4-dimethylphenol	5,000	5,000
3,5-dimethylphenol	714	333
2,4-dichlorophenol	6.5	0.65
2,5-dichlorophenol	0.45	3.3

[a]Lowest perceptible by a panel of two to four individuals

Difficulty in developing analytical techniques for the separation of phenolic substances in water supplies was a factor in attributing odors and bad taste in water to phenol alone. The distilled 4-aminoantipyrine method measured all substances which react with the reagent to form a dye. Even though it was recognized that the technique was non-specific, it became customary to report results as phenol. As late as 1967, Faust and Mikulewicz presented data which showed the limitations of the analytical application of 4-aminoantipyrine for the determination of phenols in water and waste water. Literature published before 1965 does not contain quantitative or qualitative information on 2,4-dimethylphenol in water.

Analytical techniques have been developed which enable the investiagtor to separate and identify all of the methylphenol and dimethylphenol isomers. Freedman and Charlier (1964) developed a procedure for gas liquid chromatographic separation of the low-boiling phenols (180° to 240°C). The retention times of 3,5- and 2,4-dimethylphenol were 18.2 and 18.8 minutes, respectively. Goren-Strul, et al. (1966) developed methods of extraction to separate compounds found in dilute aqueous solutions and identified the phenols by gas liquid chromatography, paper chromatography, and spectrophotometry. Hrivnak (1970) achieved good separation of the dimethylphenols by using a phosphoric acid additive for gas chromatographic analysis on open tubular columns. From 1970 to 1978 a number of techniques were published for separation, identification, and quantitation of substituted phenols (Eichelberger, et al. 1970; Cooper and Wheatstone, 1973; Dirmikis and Darbre, 1974; Brady and Pettitt,

1974; Murray, 1975; Veith and Austin, 1976; Dietz, et al. 1976; Husain, et al. 1977; Bartle, et al. 1977; Buryan, et al. 1978). Some of these techniques did not separate 2,4-dimethylphenol satisfactorily from at least one isomer. High pressure liquid chromatography appears to be the most efficient method for separating and identifying isomeric alkylphenols found in water supplies (Husain, et al. 1977). There are additional analytical techniques published which are not listed here.

In 1968, Maazik reported that large amounts (800 kg daily) of dimethylphenols were discharged into the Purtse River in Finland. The presence of dimethylphenols in public water supplies was not reported.

Phenol, 2- and 3-methylphenol, and 2,4-dimethylphenol were identified in samples of raw and treated water (Goren-Strul, et al. 1966). The sources of raw surface water and treated waters of two unspecified plants were not named in this study conducted in the Netherlands.

The amounts of 2,4-dimethylphenol in drinking water will vary according to the concentration of the compound in untreated water and the efficiency of water treatment systems in removing phenolic compounds. No data were found which estimated the ingestion by humans of 2,4-dimethylphenol in drinking water.

Ingestion from Food

Dimethylphenols have been identified as naturally-occurring constituents of some plants: tea (Kaiser, 1967), tobacco (Baggett and Morie, 1973; Spears, 1963), marijuana (Hoffmann, et al. 1975), and a conifer (Gornostaeva, et al. 1977). Although evidence is lacking that the compound occurs in

a great number of plants used for food, it is safe to assume that small amounts are ingested.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 150 was obtained for 2,4-dimethylphenol using bluegills

containing about 1 percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 2,4-dimethylphenol and the edible portion of all aquatic organisms consumed by Americans is calculated to be 150 x 2.3 = 340.

Inhalation

No literature was found which indicated that humans are exposed to 2,4-dimethylphenol except as components of complex mixtures. Even though adverse health effects have been reported due to the exposure of workers to complex mixtures containing dimethylphenols, the compounds were present in low concentrations relative to other hydrocarbons and the adverse effects were not attributed to dimethylphenols (NIOSH, 1978). Health effects observed following inhalation exposures to cresol vapors (Corcos, 1939) are similar to those observed in the chronic exposure of rats to orally administered 2,6- or 3,4-dimethylphenol (Maazik, 1968).

Many workers are exposed by inhalation to commercial degreasing agents which contain methylphenols and dimethylphenols. No adverse health effects have been reported to date (NIOSH, 1978).

The compound 2,4-dimethylphenol has been identified in cigarette smoke condensate (Smith and Sullivan, 1964; Hoffmann and Wynder, 1963; Baggett and Morie, 1973). Concentrations in smoke condensates from six different brands

of American cigarettes ranged from 12.7 to 20.8 mg per cigarette with filters removed, and 4.4 to 9.1 mg per cigarette with filters in place (Hoffmann and Wynder, 1963). The compound has also been identified in the smoke of marijuana cigarettes (Hoffmann, et al. 1975).

Combustion and pyrolysis of building materials containing phenolic resin produce phenol, 2- and 3-methylphenol, 2,4- and 2,6-dimethylphenol and 2,4,6-trimethylphenol approximately in descending order of quantity (Tsuchiya and Sumi, 1975). Phenolic resins are used in the building industry as foam insulation and adhesives in laminates. Combustion of such materials would expose humans to 2,4-dimethylphenol.

A quantitative estimate cannot be made of the amounts of 2,4-dimethyl-phenol inhaled by the general population. When enough data are available, it should be possible to estimate the exposure of the smoking population.

Dermal

The ability of cresols to be absorbed through the skin and produce local and systemic effects has been demonstrated in humans (Herwick and Treweek, 1933; Cason, 1959; Green, 1975). The skin is considered to be the primary route of occupational exposure to complex mixtures containing 2,4-dimethylphenol. In addition to workers exposed in petroleum, coal and coke processing, and degreasing operations, the general public uses many commercial products containing complex mixtures of phenol and the mono- and dimethylphenols.

PHARMACOKINETICS

Absorption

Uzhdovini, et al. (1974) determined that all of the dimethylphenol isomers produced necrosis when applied in a molten state to rat skin. Only 2,4-dimethylphenol was lethal in the molten state; the LD50 was 1040 mg per kg. In only one case was an isomer reported to be applied in a solvent, namely 2,6-dimethylphenol in ethanol. In this instance, the solubilized compound was lethal, with an LD50 of 920 mg per kg.

In mouse skin bioassays, Boutwell and Bosch (1959) tested five of the six dimethylphenol isomers (2,3-dimethyl-

phenol was not tested) and observed that irritation and hair loss paralleled the ability of each compound to promote a carcinogenic response to a single subcarcinogenic dose of dimethylbenzathracene (DMBA). A 20 percent solution of the 2,4-dimethyl isomer in benzene applied 2 times a week was the most active promoting agent among the isomers. In these bioassays, phenol was more damaging to the skin and more active than 2,4-dimethylphenol in initiating and promoting skin carcinomas when applied in equal concentrations.

These results from animal studies suggest that the 2,4-dimethyl isomer is readily absorbed through the skin and that other phenolic compounds contained in complex mixtures must be considerd when attempting to set standards safe for the exposure of humans to 2,4-dimethylphenol.

Distribution

No literature was found showing the distribution of 2,4-dimethylphenol in humans or animals. In an 8-month chronic study of rats orally administered 2,6-or 3,4-dimethylphenol, pathological damage was observed in the liver, spleen, kidneys, and heart; distribution through these organs of 2,6- or 3,4-dimethylphenol (and/or their metabolites) can be postulated (Maazik, 1968).

Metabolism

In 2 to 3 kg female rabbits, the pattern of metabolism of the six isomers of dimethylphenol was shown to be quite similar (Bray, et al. 1950). In a single oral dose of 850 mg of 2,4-dimethylphenol, 8 to 16 percent was excreted conjugated with sulfuric acid and 50 to 72 percent with glucuronic acid. A small proportion was also hydroxylated, but was not identified. Observations obtained from identifi-

TABLE 3

Urinary Excretion of Metabolites of 2,4-Dimethylphenol[a] in the Rabbit (Bray, et al. 1950)

Metabolic Product	% of Dose Administered	
	Range	Average
Free non-acidic phenol	0-5	2
Ethereal sulphate	12-14	13
Ester glucuronide	-04	1
Ether glucuronide	35-56	46
Ether-soluble acid	49-75	64

[a]A dose of 850 mg administered by stomach tube.

cation of the metabolites of 2,4-dimethylphenol in urine are reported in Table 3.

In 1967, Gilbert, et al. showed that microsomal enzymes are induced in the liver by pretreatment of weanling rats with 2,4-dimethylphenol (1.5 millimoles per kg). The activities of hexobarbitone oxidase and aminopyrine demethylase were measured in microsomal fractions derived from the livers of treated and untreated animals. It was observed that the inducing capacity of a compound was stimulated by the presence of an alkyl substituent in position 4.

The metabolism of 2,4-dimethylphenol has been studied in a Pseudomonas species isolated from river mud (Chapman and Hopper, 1968). Metabolism was initiated by the oxidation of the methyl group in position 4 relative to the hydroxyl group. Three intermediates identified were 4-hydroxy-3-methylbenzoic acid, 4-hydroxyisophthalic acid, and protocatechuic acid.

Excretion

The excretion of metabolites of 2,4-dimethylphenol was studied in rabbits by Bray, et al. in 1950. The pattern of metabolism of the six isomers was quite similar and only the results for the 2,4-isomer are reported in Table 3. These data indicate rapid metabolism and excretion. Analytical techniques of the 1950's made the quantitation of metabolites difficult.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The germicidal activity of phenol and substituted phenols was recognized more than 50 years ago (Schaffer and Tilley, 1927). Data were presented which compared the germicidal

activity of 2,4-dimethylphenol and other substituted phenols to the activity of phenol. The phenol coefficient was based on the relative amount of phenol required to kill the test organism in the same length of time as the test compound. Using Bacillus typhosus as the test organism, the phenol coefficient of 2,4-dimethylphenol was 5.8.

Woodward, et al. (1934) reported data from testing 37 derivatives of phenol for their fungicidal activity. Dialkyl compounds were more powerful fungicides than the corresponding monoalkyl compounds. In comparison to phenol (1.0) the fungicidal activity of 2,4-dimethylphenol was 6.3 in experiments with the yeast, Monilia tropicalis.

In 1975, Leifertova, et al. studied the relationship between the biological activity of phenolic compounds as antifungal and antibacterial agents and the chemical structure of the compounds. The dialkyl- and trialkylphenols were the most active. Activity was increased when alkyl groups were in the 2- and 4-position as in 2,4-dimethylphenol.

Dimethylphenols and methylphenols were among compounds tested as a chemotherapeutic treatment to selectively destroy plant neoplasms without injuring normal plant tissues (Schroth and Hildebrand, 1968). Solutions were applied with a swab to tumors and surrounding areas. The most selective of the methylated phenols tested were 3-methylphenol and 2,4-dimethylphenol. At concentrations of 1.5 percent (v/v), 60 to 80 percent of tumor tissues (2 to 2.5 cm in diameter) on tomato plants were destroyed with little injury to adjacent stem tissues. The compounds that indicated

selectivity in destroying plant neoplasms were further studied for their activity in killing bacterium responsible for producing neoplastic growth in plants (Agrobacterium tumefaciens). At 0.6 percent, 2,4-dimethylphenol was bacteriocidal to this organism.

Ascites sarcoma BP8 cells, cultured in suspension in vitro, were used to study the toxicity of more than 250 compounds which have been identified in tobacco and tobacco smoke (Pilotti, et al. 1975). Phenol, methylphenols, and dimethylphenols all inhibited the growth of cells; among these compounds, 2,4-dimethylphenol was most active (Table 4). The moderate toxicity of phenol to BP8 cells was increased by the introduction of electron-donating substituents such as alkyl groups.

The acute toxicity of phenol, methylphenols, and dimethylphenols in 422 mice and 289 rats was reported in 1974 by Uzhdovini, et al. The number of animals used for each experiment was not reported. Compounds were administered by inhalation, intubation, intraperitoneal injection, or by application to the skin.

TABLE 4

Inhibition of Ascites Sarcoma BP8 Cell Culture Growth Rate By Phenol and Methylated Phenols (Pilotti, et al. 1975)

Compound	Percent Inhibition	
	1 mM	0.1 mM
Phenol	25	5
2-methlphenol	56	7
3-methylphenol	31	5
4-methylphenol	93	13
2,3-dimethylphenol	78	2
2,4-dimethylphenol	99	11
2,5-dimethylphenol	74	0
2,6-dimethylphenol	79	5
3,4-dimethylphenol	75	5
3,5-dimethylphenol	44	7

Uzhdovini, et al. (1974) reported that inhalation of dimethylphenol vapors at "levels of hundred of milligrams per liter" did not cause death in the animals. A mixture of vapors and aerosols led to the death of mice. The only LC50 reported was 0.179 mg per liter for 2-methylphenol. The investigators reported that aerosols condensed in the chamber and deposited on the walls and skin of the animals. Toxic effects were attributed to penetration of compounds through the skin. Signs observed during inhalation included irritation of mucous membranes, enlargement of blood vessels of the ears and extremities, and excitation followed by lethargy.

Ten percent solutions of each compound in oil were intubated into the stomachs of animals to test the acute toxicity of ingested compounds (Uzhdovini, et al. 1974). As shown in Table 5, LD50 data indicated that dimethylphenols were less toxic than phenol and methylphenols in mice. In rats, 2,4-dimethylphenol was the least toxic.

Solutions of 2,6-dimethylphenol were injected intraperitoneally into mice (Uzhdovini, et al. 1974). In these experiments each group consisted of 10 mice. The LD50 following injection of 10 percent 2,6-dimethylphenol in oil was 271 mg per kg; for a 0.1 percent solution of 2,6-dimethylphenol in water the LD50 was 232 mg per kg. When the same concentration (0.5 percent) of 2,6-dimethylphenol was administered in oil or water, the toxicity of the water solution was greater than the oil solution. Following a dose of 300 mg per kg, 60 percent ($\pm$ 15.4) of the mice died that received the aqueous solution and 20 percent ($\pm$ 12.6) died after injection of the solution in oil. Apparently more than

one group of mice was dosed per treatment; the number of groups was not reported.

The application of molten or crystalline compounds to the skin of rats produced necrosis on contact. Molten methylphenols and 2,4-dimethylphenol were lethal (Table 6). Solid dimethylphenols (2,5-; 2,6-; 3,4; 3,5) and molten 2,6-dimethylphenol did not produce fatal toxicity in rats; however, an ethanol solution of 2,6-dimethylphenol was lethal for mice, with an LD50 of 920 mg per kg.

Uzhdovini, et al. (1974) concluded that the greatest danger of poisoning to man is by absorption through the skin. In general the dimethylphenols and 3-methylphenol are less acutely toxic than the 2-and 4-methylphenols.

Maazik (1968) presented data on the short-term toxic effects of four dimethylphenol isomers (2,5-; 2,6-; 3,4-; 3,5-). Even though 2,4-dimethylphenol was not used as a test compound, Maazik's observations will be summarized because of the limited data on the toxicity of dimethylphenols in mammals. Compounds were administered in a single dose by mouth in the form of finely dispersed aqueous suspensions, and the animals were observed for 15 days. LD50 for white mice and albino rats was determined by probit analysis as modified by Prozorovskii (1962); for rabbits, LD50 was determined by Deichmann and LeBlanc in 1943 (Table 7). The clinical signs of acute poisoning were dyspnea, disturbance of motor coordination, rapid onset of clonic spasms, and asymmetrical body position. Most of the animals died within 24 hours.

Guinea pigs were relatively insensitive to the dimethylphenols (Maazik, 1968). Administration of 2,115 mg per

TABLE 5

Acute Toxicity of Phenol and Methylated Phenols[a]
Uzhdovini, et al. 1974)

Compound	LD50 (mg/kg) with Confidence Limits[b]	
	Mice	Rats
phenol	436 (311-610)	-
2-methlphenol	344 (270-436)	1470 (1170-1830)
3-methlphenol	828 (695-985)	2010 (1240-3200)
4-methlphenol	344 (266-433)	1460 (1260-1670)
2,4-dimethlphenol	809 (724-914)	3200 (2780-3680)
2,5-dimethlphenol	1140 (797-1530)	1270[c]
2,6-dimethlphenol	980 (823-1166)	1750 (1420-2150)
3,4-dimethlphenol	948 (658-1365)	1620
3,5-dimethlphenol	836 (733-906)	1915[c]

[a]Intubated into the stomach 10% in oil.
[b]LD50 according to Prozorovskii, 1962; figures in parentheses interpreted as extreme values observed.
[c]LD50 according to Deichmann and LeBlanc, 1943.

TABLE 6

Acute Toxicity of Methylated Phenols Applied to the Skin of Rats (Uzhdovini, et al. 1974)

Compound[a]	LD50 (mg/kg) with Confidence Limits[b]
2-methlphenol	620 (370-1110)
3-methlphenol	110 (800-1400)
4-methlphenol	750 (510-1100)
2,4-dimethlphenol	1040 (630-1716)

[a] Compounds were described as "molten"
[b] Values in parentheses interpreted as extreme values observed

TABLE 7

Toxicity of Dimethlphenol Isomers in Animals Following A Single Peroral Dose (mg/kg) (Maazik, 1968)

Isomer	LD50 ± SE		LD50
	White Mice	Albino Rats	Rabbits
2,5-dimethylphenol	383 ± 36	444 ± 26	938
2,6-dimethylphenol	479 ± 47	296 ± 36	700
3,4-dimethylphenol	400 ± 43	727 ± 70	800
3,5-dimethylphenol	477 ± 49	608 ± 44	1,313

kg of 2,6-dimethylphenol caused signs of poisoning but these disappeared after 10 minutes. Administration of 1,200 mg per kg of 3,4-dimethylphenol caused only mild poisoning.

In longer-term experiments, 30 male albino rats, divided into three groups of 10, received perorally for 10 weeks 29.5 mg per kg 2,6-dimethylphenol, 72.5 mg per kg 3,4-dimethylphenol, or no treatment (Maazik, 1968). Since the doses were described as being 0.1 of the LD50 for albino rats, the reporting of doses in the publication as ug amounts is concluded to be an error. Animals treated with 2,6-dimethylphenol exhibited a depressed weight gain in comparison to controls and increased weight coefficients of the liver and spleen. Rats treated with 3,4-dimethylphenol exhibited a statistically significant lag in weight gain and a statistically significant increase of the weight coefficients of the spleen, heart, and lungs. Histological examination revealed marked atrophy and parenchymatous dystrophy of the hepatic cells in both experimental groups. No differences were observed in the morphological picture of the blood, prothrombin time, ratios of the serum protein fractions, or the concentration of phenol in the urine.

A long-term experiment was performed with 53 male albino rats, using 6 or 0.06 mg per kg of 2,6-dimethylphenol, and 14 or 0.14 mg per kg of 3,4-dimethylphenol; the doses represent 2×10^{-2} and 2×10^{-4}, respectively of the LD50 for rats (Maazik, 1968). The compounds were administered perorally for 8 months. No significant differences were noted in animals receiving the lower doses. Some of the effects of higher doses are summarized in Table 8. Pathological changes observed in animals receiving the high dose of dimethylphenols

included fatty dystrophy and atrophy of the hepatic cells, hyaline-droplet dystrophy in the kidneys, proliferation of myeloid and reticular cells, atrophy of the lymphoid follicles of the spleen and parenchymatous dystrophy of heart cells.

The 2,4-isomer is known to be an ATP blocking agent and as such has been used as an experimental tool. Hauge, et al. (1966) observed the development of vasoconstriction in isolated blood-perfused rabbit lung preparations as a function of time or arterially injected ATP (50 μg). Vasoconstriction resulting from physiological causes or added ATP was "surprisingly" inhibited by the addition of a commercial preparation of tri-cresol which was found to contain phenol, methylphenols, and dimethylphenols.

In 1968, Lunde, et al. reported the effects of the individual compounds found in tri-cresol on vasoconstriction in the isolated perfused lung. The effectiveness of the substituted phenols in inhibiting vasoconstriction was related to the position of the methyl groups relative to the hydroxy group. Among the dimethylphenol isomers, 2,4- and 2,6-were the most effective in inhibiting vasoconstriction; 2,3-, 2,5-, and 3,4- were less effective, and 3,5- had no effect. Inhibition of vasoconstriction can be reversed by additional ATP. In this section, the mechanism of ATP-induced vasoconstriction and 2,4-dimethylphenol inhibition of vasoconstriction is unknown. Lunde, et al. (1968) suggested that the most likely explanation is that the 2,4-dimethylphenol directly inhibits the effect of ATP on smooth muscle at a receptor level.

In a study of the role of histamine in hypoxic pulmonary hypertension in the rat, Hauge (1968) showed that semicarbazide, a histaminase inhibitor, potentiated the induced hypoxic vasoconstrictor response in isolated and ventilated lungs perfused with homologous blood. This response was blocked by 2,4-dimethylphenol at 1 to 10 mg. This demonstration of physiological activity indicates that the compound may cause adverse health effects in humans as a result of chronic exposure.

Synergism and/or Antagonism

Apart from the tumor-promoting activity of 2,4-dimethylphenol (Boutwell and Bosch, 1959), data were not found concerning compounds which compete with or enhance the biological activity of 2,4-dimethylphenol.

Teratogenicity and Mutagenicity

No investigations of the teratogenic or mutagenic potential of 2,4-dimethylphenol were found in the literature. Boutwell and Bosch (1959) presented data which showed carcinogenic and tumor promoting effects of four dimethylphenol isomers.

Phenol was mutagenic to E. coli strain B/Sd-4 (Demerec, et al. 1951) and in Drosophila after exposing isolated gonads in vitro and implanting them into host larvae (Hadorn and Niggli, 1946). Levan and Tjio (1948a; 1948b) observed C-mitosis in root tips of Allium cepa exposed to phenol or methylphenol isomers, but chromosome fragmentation was rare.

TABLE 8

Toxic Effects of Dimethylphenol Administered Perorally for 8 Months (Maazik, 1968)

Compound	Dose	Observation
2,6-dimethylphenol	6 mg/kg	Significant decrease in blood serum SH. Decrease in blood pressure. Increase in concentration of SH groups in liver, spleen, and brain. Pathological changes in liver, spleen, kidneys, and heart.
3,4-dimethylphenol	14 mg/kg	Decrease in blood serum SH. Decrease in erythrocytes and hemoglobin. Increase in concentration of SH groups in liver, spleen, and brain. Pathological changes in liver, spleen, kidneys, and heart.

Carcinogenicity

Boutwell and Bosch (1959) reported that 2,4-dimethylphenol in high concentrations produced papillomas and carcinomas on the skin of tumor-susceptible female mice of the Sutter strain. Five mg in benzene (25 ul of 20 percent 2,4-dimethylphenol) applied twice weekly produced carcinomas in 12 percent of 26 mice at 28 weeks (Table 9). In this experiment, benzene alone was not evaluated; the only data related to benzene itself refer to a test of its promoting activity following a subcarcinogenic dose of DMBA. In this experiment, benzene was applied twice weekly to the skin of mice after a single application of 75 ug DMBA in benzene; observation at 24 weeks of the 27 surviving mice showed no carcinomas and an 11 percent incidence of papillomas.

In the 1959 study done by Boutwell and Bosch, over 50 different compounds related to phenol were tested for their ability to initiate or promote the appearance of tumors. (Only those results with compounds closely related to 2,4-dimethylphenol are reported here.) In these experiments, 2,4-dimethylphenol was shown to promote the appearance of papillomas and carcinomas after a single subcarcinogenic application of DMBA. Animals were selected at random from a common pool of 2- to 3-month old female Sutter mice. The fur was shaved from the test area of the mid-dorsal region of mice about 1 week prior to the first application of the test substance. Because of the possibility of mechanical irritation and damage to papillomas, the mice were not shaved again after the experiment was started. A single application of 75 ug DMBA (25 ul of 0.3 percent in benzene)

TABLE 9

Carcinogenic Effects of Dimethylphenol and Phenol on Mouse Skin (Boutwell and Bosch, 1959)

Agent in Benzene	Amount Twice Weekly in 25 ul (mg)	Duration (weeks)	No. of Survivors/ Original	Average Pa[a]/ survivor	Percent Survivors with Pa[a]	Percent Survivors with Ca[b]	
2,4-dimethylphenol	5.0	24	19/24	1.42	63	5	(42 at 39 wk
	2.5	20	26/29	0.66	31	0	(12 at 28 wk
3,5-dimethylphenol	2.5	20	22/30	0.91	55	5	(14 at 28 wk
3,4-dimethylphenol	2.5	20	28/29	0.71	50	4	(14 at 28 wk
2,5-dimethylphenol	2.5	20	25/30	0.40	24	0	(8 at 28 wk)
2,6-dimethylphenol	2.5	20	26/30	0.15	8	0	
phenol	5.0	24	20/33	2.25	90	15	(65 at 40 wk
	2.5	24	19/33	2.68	95	37	(68 at 39 wk
	2.5	20	24/30	0.62	33	13	(29 at 28 wk
	1.25	24	25/33	1.16	56	4	(12 at 40 wk

[a] Papilloma
[b] Carcinoma

was given; after one week, the promoting agent in a solvent was applied twice weekly for the duration of the experiment. The gross identifications of benign and malignant tumors were confirmed periodically by microscopic examination. Five mg of 2,4-dimethylphenol in benzene (25 ul of 20 percent), applied twice a week after a single application of 75 ug DMBA, elicited a carcinogenic response in 18 percent of the mice at 23 weeks (Table 10). All four of the dimethylphenol isomers promoted the appearance of papillomas and carcinomas; 2,4-dimethylphenol was the most active. Results reported with phenol as the promoting agent (Table 13) suggest that the selection of solvents for the initiator and promotor may alter the biological response.

The cresol isomers (2-, 3-, and 4-methylphenol) tested by Boutwell and Bosch (1959) did not promote carcinogenesis in animals at 12 weeks. Five mg of a cresol isomer in acetone was applied twice weekly to the backs of mice initiated with a subcarcinogenic dose of DMBA (75 ug) in acetone. At 12 weeks the incidence of papillomas observed in the survivors ranged from 35 to 59 percent.

Phenolic fractions of cigarette smoke condensate have been shown to promote carcinogenesis in mouse skin bioassays (Lazar, et al. 1966; Bock, et al. 1971; Roe, et al. 1959). Phenol and methylphenols were contained in the fraction in ug per cigarette; therefore the carcinogenic promoting action cannot be directly ascribed to 2,4-dimethylphenol alone.

No reports of epidemiologic studies of workers exposed to 2,4-dimethylphenol were found in the literature. It is unlikely that any segment of the population is exposed

to this compound alone. Large segments of the population are exposed to small amounts of 2,4-dimethylphenol in complex mixtures in petroleum and coke oven industries, commercial cresol, cigarettes, and commercial products using fractions obtained from coal tar acids and petroleum distillates.

No data were found relating the exposure of humans to 2,4-dimethylphenol to the incidence of cancer. In general, the complex mixtures in which 2,4-dimethylphenol is often present are so toxic that contact is avoided when the toxicity of the mixture is known.

TABLE 10

Carcinogenic Promoting Effects of Dimethylphenol and Phenol on Mouse Skin Following the Single Application of 75 ug DMBA (Boutwell and Bosch, 1959)

Promoting Agent in Benzene	Amount Twice Weekly in 25 ul (mg)	Duration (weeks)	No. of Survivors/ Original	Average Pa[a] Survivor	Percent Survivors with Pa[a]	Percent Survivors with Ca[b]	
None	(Benzene control)	24	27/32	0.15	11	0	
2,4-dimethylphenol	5.0	15	28/30	1.21	50	11	(18 at 23 wk)
3,4-dimethylphenol	5.0	15	21/30	2.66	95	0	(14 at 23 wk)
2,6-dimethylphenol	5.0	15	27/30	0.44	30	4	(11 at 23 wk)
3,5-dimethylphenol	5.0	15	20/30	0.90	40	0	(5 at 23 wk)
phenol	5.0	24	10/33	3.20	100	20	(70 at 38 wk)
	2.5	24	15/33	3.94	100	33	(93 at 39 wk)
	1.75	24	27/33	1.67	74	4	(26 at 40 wk)
phenol[c]	5.0	12	22/27	1.50	64	0	
phenol[d]	5.0	12	21/24		58	5	

[a] Papilloma
[b] Carcinoma
[c] Initiator, 75 ug DMBA in acetone
[d] Initiator and promotor in acetone

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not been promulgated for 2,4-dimethylphenol for any sector of the environment or workplace.

Current Levels of Exposure

Data are not available for estimating the exposure of humans to 2,4-dimethylphenol.

Special Groups at Risk

Workers involved in the fractionation and distillation of petroleum or coal and coal tar products comprise one group at risk. Workers who are intermittently exposed to certain commercial degreasing agents containing cresol may also be at risk. Cigarette and marijuana smoking groups and those exposed to cigarette smoke inhale ug quantities of 2,4-dimethylphenol.

Basis and Derivation of Criterion

In quantitative assessment of carcinogenicity, there are a number of special conditions which render the extrapolation of animal carcinogenesis data to man inappropriate (See Methodology Document). In the present case, the condition which applies is that the route of administration is inappropriate in terms of conceivable human exposure.

Only one study was found which indicated that 2,4-dimethylphenol could be carcinogenic in mammals; Sutter mice, a strain highly susceptible to skin carcinomas, were used (Boutwell and Bosch, 1959). In these experiments, 5 mg or 2.5 mg of 2,4-dimethylphenol in benzene, applied twice a week to the backs of shaved mice, produced papillomas and carcinomas of the skin at the site of application. Even though the compound is known to be rapidly absorbed,

systemic effects or internal tumors were not reported. Additionally, the possible contribution of other chemicals to the response observed cannot be discounted. A solvent control (benzene) was not run, and the mice were housed in wood cages treated with creosote, which may have initiated the carcinogenic response (personal communication with Dr. Boutwell, 1978).

In addition, the Carcinogen Assessment Group, U.S. EPA, Washington, D.C. concluded that the data in Boutwell and Bosch "regarding possible carcinogenic effects (via initiation) of 2,4-dimethylphenol are inconclusive. The report did indicate that 2,4-dimethylphenol was a promoting agent. Although promoters have a potential carcinogenic risk to humans, there is no dose-response data with which to formulate a quantitative risk extrapolation."

Is is inappropriate to extrapolate from results obtained from the use of high concentrations in skin painting studies to an estimate of the possible carcinogenic effects of the ingestion of small amounts of 2,4-dimethylphenol in water. The only data found for the ingestion of 2,4-dimethylphenol were an LD50 for mice of 809 mg per kg, and an LD50 for rats of 3,200 mg per kg (Uzhdovini, et al. (1974).

The National Academy of Sciences in a 1977 publication concerning drinking water and health concluded the following:

> 2,4-Dimethylphenol appears to be a topical cocarcinogen, but its role as a primary cancer-producing agent is uncertain. Its potential role in cancer production warrants consideration of further testing. An in vitro mutagenicity assay should be carried out to further evaluate its mutagenic potential.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long-term oral toxicity of 2,4-dimethylphenol, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water are established.

We recommend that a criterion should not be set for 2,4-dimethylphenol in water until definitive data are obtained. In order to protect public health, exposure of humans to this compound should be minimized.

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